MT-ND4 gene

mitochondrially encoded NADH:ubiquinone oxidoreductase core subunit 4

Normal Function

The *MT-ND4* gene provides instructions for making a protein called NADH dehydrogenase 4. This protein is part of a large enzyme complex known as complex I, which is active in mitochondria. Mitochondria are structures within cells that convert the energy from food into a form that cells can use. These cellular structures produce energy through a process called oxidative phosphorylation, which uses oxygen and simple sugars to create adenosine triphosphate (ATP), the cell's main energy source.

Complex I is one of several enzyme complexes necessary for oxidative phosphorylation. Within mitochondria, these complexes are embedded in a tightly folded, specialized membrane called the inner mitochondrial membrane. During oxidative phosphorylation, mitochondrial enzyme complexes carry out chemical reactions that drive the production of ATP. Specifically, they create an unequal electrical charge on either side of the inner mitochondrial membrane through a step-by-step transfer of negatively charged particles called electrons. This difference in electrical charge provides the energy for ATP production.

Complex I is responsible for the first step in the electron transport process, the transfer of electrons from a molecule called NADH to another molecule called ubiquinone. Electrons are then passed from ubiquinone through several other enzyme complexes to provide energy for the generation of ATP.

Health Conditions Related to Genetic Changes

Leber hereditary optic neuropathy

Several mutations in the *MT-ND4* gene are known to cause Leber hereditary optic neuropathy. Each of these mutations changes a single protein building block (amino acid) in the NADH dehydrogenase 4 protein. One *MT-ND4* mutation is the most common cause of Leber hereditary optic neuropathy; it is responsible for about 70 percent of all cases worldwide. This mutation, which can be written as G11778A or Arg340His, replaces the amino acid arginine with the amino acid histidine at protein position 340. This mutation tends to cause severe vision loss, with little chance of recovery.

Researchers are investigating how mutations in the *MT-ND4* gene lead to Leber hereditary optic neuropathy. These genetic changes appear to prevent complex I from interacting normally with ubiquinone, which may affect the generation of ATP. *MT-ND4* mutations may also increase the production within mitochondria of

potentially harmful molecules called reactive oxygen species. It remains unclear, however, why the effects of these mutations are often limited to the nerve that relays visual information from the eye to the brain (the optic nerve). Additional genetic and environmental factors probably contribute to the vision loss and other medical problems associated with Leber hereditary optic neuropathy.

Leigh syndrome

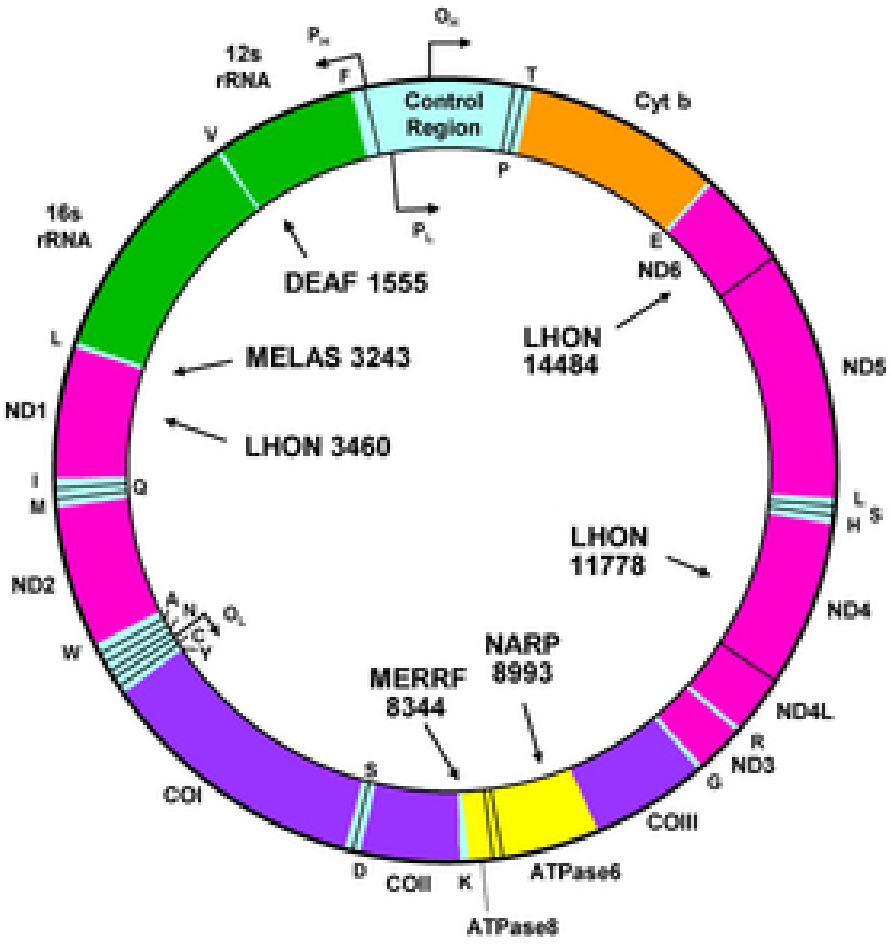
other disorders

A mutation in the *MT-ND4* gene also has been identified in a small number of people with Leigh syndrome, a progressive brain disorder that typically appears in infancy or early childhood. Affected children may experience vomiting, seizures, delayed development, muscle weakness, and problems with movement. Heart disease, kidney problems, and difficulty breathing can also occur in people with this disorder.

The *MT-ND4* mutation that can cause Leigh syndrome, written as C11777A or Arg340Ser, replaces the amino acid arginine with the amino acid serine at protein position 340. This genetic change appears to disrupt the normal function of complex I in mitochondria. It is not known, however, how this *MT-ND4* mutation is related to the specific features of Leigh syndrome.

Chromosomal Location

Molecular Location: base pairs 10,760 to 12,137 on mitochondrial DNA (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Other Names for This Gene

- mitochondrially encoded NADH dehydrogenase 4
- MTND4
- NADH dehydrogenase 4
- NADH dehydrogenase subunit 4

- NADH-ubiquinone oxidoreductase chain 4
- NADH-ubiquinone oxidoreductase, subunit ND4
- ND4
- NU4M_HUMAN

Additional Information & Resources

Educational Resources

- Mayo Clinic Mitochondrial Disease Biobank
  http://www.mayo.edu/research/centers-programs/mitochondrial-disease-biobank/overview
- Oxidative Phosphorylation (Biochemistry, Fifth Edition, 2002)
  https://www.ncbi.nlm.nih.gov/books/NBK21208/
- The Neuromuscular Disease Center at Washington University: Complex I
  http://neuromuscular.wustl.edu/pathol/diagrams/mito.htm#complexI

GeneReviews

- Leber Hereditary Optic Neuropathy
  https://www.ncbi.nlm.nih.gov/books/NBK1174
- Mitochondrial Disorders Overview
  https://www.ncbi.nlm.nih.gov/books/NBK1224
- Mitochondrial DNA-Associated Leigh Syndrome and NARP
  https://www.ncbi.nlm.nih.gov/books/NBK1173

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28MT-ND4%5BTIAB%5D%29+OR+%28mitochondrially+encoded+NADH+dehydrogenase+4%5BTIAB%5D%29%29+OR+%28%28MTND4%5BTIAB%5D%29+OR+%28NADH+dehydrogenase+subunit+4%5BTIAB%5D%29+OR+%28NADH+dehydrogenase+4%5BTIAB%5D%29+OR+%28NADH-ubiquinone+oxidoreductase+chain+4%5BTIAB%5D%29+OR+%28NADH-ubiquinone+oxidoreductase,+subunit+ND4%5BTIAB%5D%29+OR+%28ND4%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1080+days%22%5Bdp%5D

OMIM

- COMPLEX I, SUBUNIT ND4
  http://omim.org/entry/516003
- LEIGH SYNDROME
  http://omim.org/entry/256000

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_ND4.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=MT-ND4%5Bgene%5D
- HGNC Gene Family: NADH:ubiquinone oxidoreductase core subunits
  http://www.genenames.org/cgi-bin/genefamilies/set/1149
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=7459
- Mitomap: Leber Hereditary Optic Neuropathy Disease Mutation Database
  http://www.mitomap.org/MITOMAP/MutationsLHON
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/4538
- UniProt
  http://www.uniprot.org/uniprot/P03905

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